SPECIAL ARTICLE

SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) Guidelines on the Management of Community-Acquired Pneumonia in Adults

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ABSTRACT

The Dutch Working Party on Antibiotic Policy (SWAB) and the Dutch Association of Chest Physicians (NVALT) convened a joint committee to develop evidence-based guidelines on the diagnosis and treatment of community-acquired pneumonia (CAP). The guidelines are intended for adult patients with CAP who present at the hospital and are treated as outpatients as well as for hospitalised patients up to 72 hours after admission. Areas covered include current patterns of epidemiology and antibiotic resistance of causative agents of CAP in the Netherlands, the possibility to predict the causative agent of CAP on the basis of clinical data at first presentation, risk factors associated with specific pathogens, the importance of the severity of disease upon presentation for choice of initial treatment, the role of rapid diagnostic tests in treatment decisions, the optimal initial empiric treatment and treatment when a specific pathogen has been identified, the timeframe in which the first dose of antibiotics should be given, optimal duration of antibiotic treatment and antibiotic switch from the intravenous to the oral route. Additional recommendations are made on the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion of CAP, on the potential benefit of adjunctive immunotherapy, and on the policy for patients with parapneumonic effusions.

KEYWORDS

Antimicrobial therapy, community-acquired pneumonia, guidelines

INTRODUCTION

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lower respiratory tract which in general develops outside a hospital or nursing home, whereby a new infiltrate is demonstrated. CAP is a common condition that carries a high burden of mortality and morbidity, particularly in the elderly.[1] The estimated annual incidence of CAP in the Western world is 5 to 11 cases per 1000 adult population.[1,2] CAP is the number one cause of death due to an infection in the developed world.[1,2]

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep Antibiotica Beleid), established by the Dutch Society for Infectious Diseases (VIZ), the Dutch Society for Medical Microbiology (NVMM) and the Dutch Society for Hospital Pharmacists (NVZA), coordinates activities in the Netherlands aimed at optimalisation of antibiotic use and containment of the development of antimicrobial resistance. SWAB and the Dutch Association of Chest Physicians (Nederlandse Vereniging van Artsen

voor Longziekten en Tuberculose, NVALT) decided to make their revisions of previously published guidelines[3,4] a combined effort, and to publish a joint guideline on the management of CAP.

The Dutch guidelines presented here describe the most relevant aspects of the antibiotic and non-antibiotic treatment of CAP. This guideline is meant for the treatment of adult patients who present at the hospital, and are treated as outpatients, as well as for hospitalised patients up to 72 hours after admission, and is in full accordance with the 2011 Dutch College of General Practitioners (NHG) practice guidelines for GPs.[5] The recommendations given are applicable to adult patients with CAP in the Netherlands, with the exception of immunocompromised patients, such as those who have undergone organ transplantation, HIV-positive patients and patients receiving immunosuppressive therapy.

METHODS AND SYSTEMIC LITERATURE REVIEW

This guideline was drawn up according to the EBRO (Evidence Based Richtlijn-Ontwikkeling) and AGREE (Appraisal of Guidelines Research and Evaluation) recommendations for the development of guidelines.[6] A review of existing (inter)national guidelines[2-5,7-12] was performed in addition to a literature search in the PubMed database, Cochrane Register of Controlled Trials (CENTRAL), EMBASE, BMJ's Best Practice® and in Sumsearch® engine. Furthermore, InforMatrix on "Antibiotic in CAP" (Digitalis Mx bv) was used. For resistance surveillance data we utilised NethMap 2010.[13] Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts delegated from the professional societies for infectious diseases (VIZ), medical microbiology (NVMM), hospital pharmacists (NVZA), pulmonary diseases (NVALT), intensive care (NVIC) and general practice (NHG). After consultation with the members of the involved professional societies, the definitive guidelines were drawn up by the delegates and approved by the boards of SWAB and NVALT. Full guideline text and literature review are available at www.swab.nl.

CAUSATIVE BACTERIAL SPECIES OF CAP IN THE NETHERLANDS AND ANTIBIOTIC SUSCEPTIBILITY

S. pneumoniae is the most commonly isolated bacterial cause of CAP in the Netherlands and should therefore always be covered in the empirical treatment. In patients with severe CAP or in patients who must be admitted to the intensive care unit, *Legionella* spp. and *S. aureus* infection are encountered more frequently in comparison with patients with mild to moderately severe CAP (*table 1*).[2,14,15] It has to be noted that in up to 50% of CAP episodes no causative microorganism can be identified.[16-21] Infection with *Coxiella burnetii* has to be considered to be an occupational and environmental hazard in endemic areas, but after the Dutch epidemic in 2007-2010, the number of new cases now seems to have again returned to the pre-epidemic level (http://www.rivm.nl/Onderwerpen/Ziekten_Aandoeningen/Q/Q_koorts).

Regarding antibiotic susceptibility, resistance of *S. pneumoniae* is highest against ciprofloxacin (up to 37%), followed by erythromycin and clarithromycin (10%), co-trimoxazole (6-14%) and doxycycline (7-12%), which limits the use of these agents for empirical treatment of CAP. Resistance of *S. pneumoniae* against penicillins is low (1-3%), of which 50% is intermediately susceptible. Resistance to levofloxacin and moxifloxacin is very uncommon (NethMap 2010[13]). In the Netherlands, it is not recommended that penicillin-resistant *S. pneumoniae* be covered by empirical therapy, except for patients who have recently returned from a country with known high prevalence of penicillin-resistant *S. pneumoniae*. Of note, 17% of *H. influenzae* strains are resistant to the combination of amoxicillin with a beta-lactamase inhibitor.[13]

Table 1. *Most common aetiologies of community-acquired pneumonia in the Netherlands*

	Patient type		
	Community	**Hospital**	**Intensive care unit**
	1 study[99*]	7 studies[16,18-20,74,78,100]	1 study[15]
S. pneumoniae	6%	25-59%	35%
H. influenzae	9%	2-15%	11%
Legionella spp.	0%	0-8%	5%
S. aureus	0%	0-5%	7%
M. catharalis	0%	2-6%	0%
Enterobacteriaceae	-	0-4%	11%
M. pneumoniae	9%	0-24%	0%
Chlamydophila spp.	2%	1-6%	-
C. burnetii	-	0-1%	-
Viral (e.g. influenza)	37%	0-22%	-
Other	2%	3-14%	10%
No pathogen identified	33%	13-51%	34%

Data derived from most recent studies and categorised per patient type. *This study included patients with a lower respiratory tract infection in general practice, no standard X-ray was performed for the diagnosis of CAP.

GUIDANCE BY SPECIFIC SYMPTOMS AND COMORBIDITY IN THE CHOICE OF INITIAL ANTIBIOTIC THERAPY

The signs and symptoms of CAP at initial presentation should not be used to predict the cause of CAP or to guide pathogen-specific empirical antimicrobial therapy for CAP. Prognostic factors such as age, co-morbidity and specific exposure are only of modest importance for the choice of initial antibiotic treatment.[22,23] There is no convincing evidence that *H. influenzae* and *M. catarrhalis* are more common causes of CAP among patients with COPD.[22,24] Therefore, it is not recommended to cover *H. influenzae* and *M. catarrhalis* in the initial treatment of CAP in patients with COPD. An exception is bronchopneumonia, in which case it is advised to cover *H. influenzae* by empirical antibiotic therapy. CAP in patients with serious structural lung disease is more frequently caused by *P. aeruginosa* when compared with patients without an underlying lung disease.[25] In the case of aspiration, anaerobes and *Enterobacteriaceae* are more often identified.[26] Prospective studies are needed to address the question whether or not it is of clinical benefit to cover anaerobes in the case of aspiration pneumonia. In the meantime, it is recommended that in those patients anaerobes and *Enterobacteriaceae* are covered by initial antibiotic therapy. CAP caused by *S. aureus* is often preceded by influenza virus infection; however the incidence of *S. aureus* pneumonia is very low in patients with non-severe CAP. In non-severe CAP it is therefore not recommended that *S. aureus* be covered by the empiric antibiotic regimen. *Legionella* infection should be considered in patients with CAP who have recently travelled abroad.[27] Penicillin resistance of *S. pneumoniae* should be considered in patients with CAP and recent stay in countries with a high prevalence of penicillin-resistant pneumoccoci. Infection with *Coxiella burnetii* should be considered in patients with CAP living in endemic areas of *C. burnetii* infection.[28,29]

SEVERITY OF DISEASE ON PRESENTATION IMPORTANT FOR CHOICE OF INITIAL TREATMENT

Patients with CAP may be classified according to severity: mild, moderate-severe and severe CAP. Selection of empiric antibiotic therapy should be guided by the severity of the disease at presentation. Three validated scoring systems are in use: the Pneumonia Severity Index (PSI or Fine score), the CURB-65 score and the CRB-65 score (*table 2*).[30-32] PSI, CURB-65 and CRB-65 are equally reliable in predicting 30-day mortality in patients hospitalised with CAP.[33-35] Alternatively, a pragmatic classification (treatment at home, admission to a general medical ward, and admission to an intensive care unit) can be used. The committee does not recommend any of the scoring systems over the others; however, we recommend that each hospital consistently uses only one of these scoring systems in daily practice.

Table 2. *Validated scoring systems to measure the severity of disease in patients with community-acquired pneumonia: the CURB-65 and Pneumonia Severity Index*[30,31]

CURB-65

CURB-65 criteria

- **C**onfusion: defined as a new disorientation in person, place or time
- **U**rea >7 mmol/l
- **R**espiratory Rate ≥30/min
- **B**lood pressure: Systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg
- Age ≥ 65

Core criteria	Score CURB-65	30-day mortality
No core criteria	0	0.7%
One core criterion	1	3.2%
Two core criteria	2	3%
Three core criteria	3	17%
Four core criteria	4	41.5%
Five core criteria	5	57%

Pneumonia Severity Index (PSI or Fine score)

Step 1. Patient with community-acquired pneumonia

If presence of any of the following proceed to step 2, if all are absent assign to risk class I:
Over 50 years of age; altered mental status; pulse ≥125/min; respiratory rate >30/min; systolic blood pressure <90 mmHg; temperature <35°C or ≥40°C and/or a history of neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, liver disease

Step 2. Point scoring system (Characteristic and points assigned)

Age: Age in years (male); Age in years –10 (female)

Coexisting conditions: Neoplastic disease + 30; liver disease + 20; congestive heart failure + 10; cerebrovascular disease +10; renal disease + 10

Physical examination: Altered mental status + 20; respiratory rate ≥30 / min + 20; systolic blood pressure <90 mmHg + 20; temperature <35°C or ≥40°C + 15; pulse ≥125 / min + 10

Laboratory and radiological findings: Arterial pH <7.35 + 30; urea ≥11.0 mmol/l + 20; sodium <130 mmol/l + 30; glucose ≥14.0 mmol/l + 10; haematocrit <30% + 10; partial oxygen pressure <60 mmHg + 10; pleural effusion + 10

Step 3. Calculation of 30-day mortality

Risk class	Total score	Mortality
I	Not applicable	0.1%
II	≤70	0.6%
III	71-90	0.9%
IV	91-130	9.3%
V	>130	27.0%

Please visit www.jniv.nl for easy calculation tools.

RADIOLOGICAL INVESTIGATIONS IN THE DIAGNOSTIC WORK-UP OF PATIENTS SUSPECTED FOR CAP

The chest X-ray does not allow prediction of the causative microorganism in CAP.[21,36,37] In patients with a clinical suspicion of CAP the sensitivity of the initial chest X-ray compared with high-resolution computed tomography as the reference test ranges from approximately 60% in the primary care setting to 70% in hospital care settings.[38-40] However, it is not recommended that CT scanning be performed routinely in the diagnostic workup of patients with CAP. In patients with clinical features of CAP but without signs of infection on the initial chest X-ray, an additional chest X-ray within 48 hours may help to establish the diagnosis of CAP.[41]

MICROBIOLOGICAL INVESTIGATIONS AND RAPID DIAGNOSTIC TESTS

Although interpretation of Gram stains of sputum may allow early identification of the bacteriological cause of CAP, it is not recommended for guiding initial treatment. However, before starting antimicrobial therapy, blood and (if possible) sputum specimens should be obtained for culture because this can enable streamlining of antibiotic therapy once a specific pathogen has been isolated. In addition, isolating pathogens associated with CAP from blood and/or sputum allows susceptibility testing, which is important for monitoring longitudinal trends in antibiotic susceptibilities.[42] A urinary antigen test for *Legionella* spp. should be performed in all patients with severe CAP.[2,14,43,44] One should be aware that in the early stages of the disease the *Legionella* urinary antigen test may be falsely negative, especially in patients with mild pneumonia.

The pneumococcal urinary antigen test can be performed easily and quickly (<15 minutes). Reported sensitivities of this test have ranged from 65 to 92% in adult patients with definite pneumococcal pneumonia (mostly with bacteraemia), and from 27 to 74% in patients with probable pneumococcal infection (based on positive sputum results only).[45-49] In most studies the specificity of the test was determined in pneumonia caused by another pathogen and ranged around 90%.[45-49] It has to be noted that urinary pneumococcal antigens may be detectable in adult patients with exacerbations of COPD and pneumococcal carriage without pneumonia.[50] The question is whether and how to use this test in patients with (suspected) CAP. Empiric therapy for CAP should always cover pneumococci, independent of a negative or positive urinary test. On the other hand, also when the initial pneumococcal urinary antigen test is positive, one should not withhold empirical antibiotic coverage for atypical pathogens in patients with severe CAP, as the test specificity is not 100%. In the opinion of the committee, the use of the pneumococcal urinary antigen test has no direct consequences for initial antibiotic therapy in patients with non-severe CAP, but in patients with severe CAP a urinary antigen test should be performed, as a positive test – when no other pathogen is detected – can help to streamline antibiotic treatment to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached.

For the diagnosis of Q fever during the first two to three weeks after onset of illness, the preferred tests are polymerase chain reaction (PCR) on serum or plasma.[51] For the diagnosis of Q fever >3 weeks after disease onset, or when the PCR is negative, serology (emzyme-linked immunosorbent assay, immunoglobulin M, indirect immunofluorescence and CF) is the recommended test. Seroconversion or a fourfold rise in antibody titre are diagnostic of Q fever.[51] PCR results from nasopharyngeal swabs are considered the most reliable indicator for influenza virus replication in the human body.[52-54] Validated PCR tests for respiratory viruses and atypical pathogens are preferred over serological tests. Although bacterial infections are generally associated with increased expression of procalcitonin (PCT) and soluble triggering-

Table 3. *Guideline for the choice of initial therapy for community-acquired pneumonia*

Severity	Antibiotic	Route	Dose	Frequency
Mild pneumonia				
1st choice	amoxicillin	Oral	500-750 mg	q6h-q8h
2nd choice	doxycycline	Oral	100 mg (first dose 200 mg)	q24h
Moderately severe pneumonia				
1st choice	penicillin	IV	1 MU	q6h
	amoxicillin	IV	1000 mg	q6h
Severe pneumonia				
Mono-therapy	moxifloxacin *or*	IV/oral	400 mg	q24h
	levofloxacin	IV/oral	500 mg	q12h
Combination therapy	penicillin *plus*	IV	1 MU	q6h
	ciprofloxacin	IV/oral	400 mg (500 mg orally)	q12h
Combination therapy	cefuroxime *or*	IV	750-1500 mg	q8h
	ceftriaxone *or*	IV	2000 mg	q24h
	cefotaxime *plus*	IV	1000 mg	q6h
	erythromycin	IV	500-1000 mg	q6h

IV = intravenous, MU = million units; Q = every (x) hour.

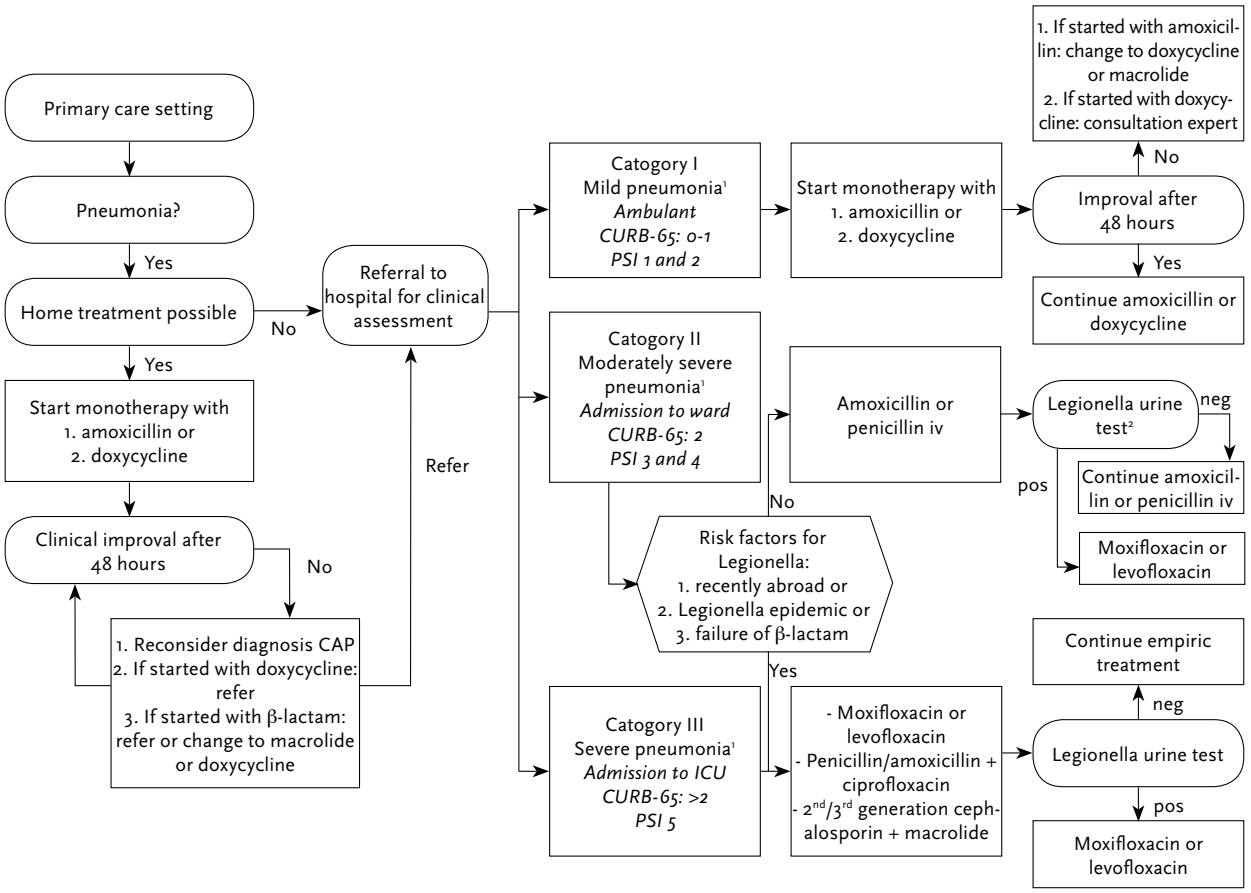
receptor-expressed-on-myeloid cells (TREM)-1, when compared with non-infectious inflammation or viral infections in the setting of CAP, their positive and negative predictive values are still ill defined and seem to be insufficient to reliably differentiate between bacterial and viral infection or to guide antibiotic therapy.[55-62]

EMPIRIC ANTIBIOTIC THERAPY FOR CAP

Risk category I (mild CAP): CURB-65: 0-1, PSI: 1-2, Pragmatic: non-hospitalised

These patients can usually be treated at home. Patients with mild CAP who are admitted to the hospital for reasons other than a strictly medical indication also

Figure 1. *Flow chart of guideline recommendations on antibiotic treatment of community-acquired pneumonia*



1• Oral macrolides should not be used as initial therapy. They can be used in the event of penicillin allergy and when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg
- In the event of penicillin allergy, give a second- or third-generation cephalosporin or moxifloxacin.
- In the event of aspiration, the possibility of anaerobes or enterobacteriacae should be taken into account: penicillin is replaced by amoxicillin-clavulanate
- In the case of fulminant pneumonia after an episode of influenza, penicillin is replaced by a beta-lactam antibiotic with activity against *S. aureus*. If CAP occurs directly following an episode of influenza, the influenza should also be treated pending results from PCR testing
- Patients with documented colonisation of the respiratory tract with *Pseudomonas* spp. receive penicillin plus ceftazidime or ciprofloxacin for category II and penicillin plus ciprofloxacin for category III
- Recommended treatment options for severe CAP (monotherapy with a fourth-generation quinolone; combination therapy with penicillin (or amoxicillin) and ciprofloxacin or combination therapy with a second- or third-generation cephalosporin and a macrolide) are considered to be three equally acceptable choices
- *Legionella* pneumonia should be treated with a fluoroquinolone. Most evidence is available for levofloxacin
- For patients with CAP who recently visited a country with a high prevalence of penicillin-resistant *S. pneumoniae* (PRPS) the dose of penicillin is increased to 2 million IU 6 dd (or continuous infusion) or 2000 mg ceftriaxone once daily is given
- A urinary antigen test for *S. pneumoniae* should be performed in all patients treated as severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to amoxicillin or penicillin once clinical stability (often within 48 hours) has been reached.

2 Always perform a Legionella urine antigen test in patients with a PSI score 4 or presence of 2 CURB-65 criteria

fall in this category. For this group, initial therapy with amoxicillin (first choice) or doxycycline (second choice) is recommended (*table 3, figure 1*). This is in accordance with the 2011 guideline for patients treated by GPs.[5] Doxycycline is not a first choice for this group in view of the 10% resistance of *S. pneumoniae* to doxycycline. The choice of a drug active against the most frequently occurring causative agent (*S. pneumoniae*) is essential in this case. Phenethicillin is not considered a first choice in view of the suboptimal gastrointestinal resorption. As a result of the increasing resistance of pneumococci to macrolides (2 to 3% in 1996 versus 10% in 2009), monotherapy with macrolides is discouraged unless there is a penicillin allergy or it is not possible to administer doxycycline (e.g. because of pregnancy or lactation). In that case, either clarithromycin or azithromycin are preferred over erythromycin, because of its gastrointestinal side effects. In pregnant women erythromycin is recommended. If there is a clinical suspicion of *Legionella* infection, then the *Legionella* urine antigen test must be carried out and empirical therapy must be adjusted. For patients in risk category I who receive amoxicillin or penicillin as initial therapy but do not improve within 48 hours, therapy should be switched to monotherapy with a macrolide or doxycycline. If therapy was initiated with doxycycline a switch to macrolides is not rational. In that case, referral to a hospital must be considered.

Risk category II (moderate-severe CAP): CURB-65: 2, PSI: 3-4, Pragmatic: hospitalised on non-ICU ward

For this category, initial therapy should be beta-lactam monotherapy, and the first choice is either intravenous penicillin or intravenous amoxicillin (*table 3, figure 1*). Doxycycline and macrolides cannot be recommended because of the increasing pneumococcal resistance. Broad-spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime are not recommended because the expected pathogens do not justify the broader spectrum. In case of a penicillin allergy, the best alternatives are a second- or third-generation cephalosporin or a fourth-generation quinolone. For patients in category II with a PSI score of 4 or 2 CURB-65 criteria, a urinary *Legionella* antigen test must be performed within 12 hours of admission. If the test is positive, therapy must be switched to monotherapy directed against *Legionella* spp. If a patient of category II has one or more of the following risk factors, initial therapy should also cover *Legionella* spp.: 1) recent visit to a foreign country, 2) coming from an epidemic setting of *Legionella* spp. infections, 3) failure to improve despite ≥48 hours treatment with a beta-lactam antibiotic at adequate dosage without evidence of abnormal absorption or non-compliance.

Risk category III (severe CAP): CURB-65: >2, PSI: 5, Pragmatic: hospitalised in ICU ward

In this group, it is recommended to always cover *S. pneumoniae* and *Legionella* spp. For this purpose there are three equally acceptable choices, all with excellent antimicrobial activity against all expected causative agents (*table 3, figure 1*). On the one hand, the choice is dependent on the risk of development of antimicrobial resistance at the population level; on the other hand, the costs, the ease of administration and the profile of side effects play an important role:

- Monotherapy with a third- or fourth-generation quinolone (levofloxacin or moxifloxacin).
- Combination therapy with penicillin (or amoxicillin) and ciprofloxacin.
- Combination therapy with a second- or third-generation cephalosporin and a macrolide.

Moxifloxacin is preferred over levofloxacin because of its high activity against pneumococci, favourable pharmacodynamic characteristics and good tissue penetration. Potential prolongation of the QT interval should be taken into account. With regard to macrolides, the unfavourable pharmacodynamics and side effects of intravenous erythromycin (including prolongation of the QT interval) should be weighed against the potential of resistance development when using quinolones.

For all patients in category III, a *Legionella* urinary antigen test should be carried out as a routine procedure within 12 hours of admission. If the test is positive, monotherapy directed against *Legionella* spp. is recommended. If the test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella* spp.) because the sensitivity of the urinary antigen test is not 100%. A urinary antigen test for *S. pneumoniae* should be performed in all patients hospitalised with severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached. Because of its low sensitivity, a negative test result does not justify broadening of empirical antibiotic therapy when no other pathogen is detected and the patient is clinically stable.

PATHOGEN-DIRECTED THERAPY

In the event of a culture-proven causative agent, pathogen-directed antibiotic treatment is to be preferred at all times (*table 4*). *Legionella* pneumonia should be treated with a fluoroquinolone. Although *in-vitro* activity of moxifloxacin is comparable with that of levofloxacin, levofloxacin has the most clinical evidence to support its use. In the case

Table 4. *Pathogen-directed therapy in community-acquired pneumonia*

Pathogen		Oral	Intravenous
S. pneumoniae	Penicillin susceptible	1 Amoxicillin 2 Phenethicillin 3 Macrolide or doxycycline[1]	1 Penicillin G 2 Amoxicillin 3 2nd or 3rd generation cephalosporin or 3rd or 4th generation quinolone[1]
	Penicillin resistance (MIC ≥2 µg/ml): agents chosen on basis of susceptibility, including cefotaxime, ceftriaxone, fluoroquinolone, vancomycin, linezolid, high-dose amoxicillin.		
H. influenzae	Non-β-lactamase producing	1 Amoxicillin 2 Macrolide or doxycycline[1]	1 Amoxicillin 2 2nd of 3rd generation cephalosporin [1]
	β-lactamase producing	1 Amoxicillin-clavulanate 2 Doxycycline or macrolide [1]	1 Amoxicillin-clavulanate 2 2nd of 3rd generation cephalosporin[1]
Legionella spp.		1 Fluoroquinolone 2 Azithromycin or clarithromycin 3 Doxycycline	1 Fluoroquinolone 2 Erythromycin
M. pneumoniae *C. psittaci* *C. pneumoniae*		1 Macrolide 2 Doxycycline	1 Macrolide 2 Doxycycline
C. burneti		1 Doxycycline 2 Ciprofloxacin	1 Doxycycline 2 Ciprofloxacin
S. aureus	Methicillin susceptible	1 Flucloxacillin 2 Amoxicillin-clavulanate 3 1st generation cephalosporin	1 Flucloxacillin 2 Amoxicillin-clavulanate 3 1st generation cephalosporin 4. Vancomycin[1] ± aminoglycoside or rifampicin
	Methicillin resistant (MRSA)	1 Vancomycin 2 Linezolid	1 Vancomycin 2 Linezolid 3 Teicoplanin ± rifampicin
P. aeruginosa		1 Ciprofloxacin	1 Ceftazidime ± aminoglycoside 2 Ciprofloxacin
K. pneumoniae		1 Amoxicillin-clavulanate 2 Trimethoprim/sulfamethoxazole	1 Amoxicillin-clavulanate 2 2nd or 3rd generation cephalosporin 3 Trimethoprim/sulfamethox
Anaerobic bacteria [2]		1 Amoxicillin-clavulanate 2 Clindamycin 3 Metronidazole	1 Amoxicillin-clavulanate 2 Clindamycin 3 Metronidazole

These recommendations are based on NethMap 2010, the Infectious Diseases Society of America, British Thoracic Society and Dutch Association of Chest Physicians (NVALT) guidelines.[2,4,14] [1]In the event of penicillin allergy; [2]Usually polymicrobial.

of *Legionella* pneumonia, there is no convincing clinical evidence for added value of adding rifampin to treatment with quinolones.[63,64]

TIMING OF FIRST DOSE OF ANTIBIOTICS, TREATMENT DURATION AND SWITCH FROM INTRAVENOUS TO ORAL ROUTE

Available literature is not convincing that prompt administration of antibiotics as soon as the diagnosis of CAP is confirmed is associated with improved clinical outcome.[65-70] For patients with severe CAP admitted through the emergency department (ED), the first antibiotic dose should be administered within four hours of presentation and preferably while still in the ED. In patients with severe sepsis and septic shock, the recommendation of the SWAB Sepsis guideline applies.[71] Although the guidelines emphasise the importance of initiating antibiotic treatment rapidly, maximal efforts should be made to avoid inaccurate diagnosis of CAP and/or inappropriate utilisation of antibiotics.

If adult patients with mild to moderate-severe CAP are treated with a beta-lactam antibiotic or fluoroquinolones, the length of antibiotic treatment can be shortened to five days in those patients who have substantially improved after three days of treatment.[72-74] As there have been no studies on the optimal duration of treatment for CAP with doxycycline, we recommend continuing seven days of treatment in these cases. Pneumonia caused by *S. aureus* should be treated for at least 14 days.[2] Pneumonia caused by *M. pneumoniae* or *Chlamydophila* spp. is generally advised to be treated for 14 days.[2] For *Legionella* pneumonia a treatment duration of seven to ten days is sufficient in

patients with a good clinical response. Of interest, two recent studies have shown that PCT measurements can be used to shorten the duration of antibiotic therapy in patients with CAP.[75,76] However, in both studies the mean duration of antibiotic therapy in the control arm was much longer (10.7 to 12 days) when compared with the standard duration of therapy as advised by this guideline (five days), therefore measurement of PCT levels to guide duration of antibiotic therapy is not recommended when standard treatment duration is limited to five to seven days.

Patients should be switched from intravenous to oral therapy when they have substantially improved clinically, have adequate oral intake and gastrointestinal absorption and are haemodynamically stable.[77-79] For patients who fulfil these criteria, inpatient observation is no longer necessary.[2,80]

THE ROLE OF ADJUNCTIVE IMMUNOTHERAPY FOR PATIENTS WITH CAP

Over the last decade a whole range of potential immunomodulating therapies as adjunctive to antibiotics have been investigated in patients with CAP. Dexamethasone as an adjunctive treatment was reported to reduce length of stay in patients with CAP, but reports are not consistent that corticosteroid therapy improved outcome in patients hospitalised with CAP.[18,81] As corticosteroid therapy is associated with – among other things – increased risk of hyperglycaemia, corticosteroids are not recommended as adjunctive therapy for the treatment of CAP. Targeting the coagulation system by administration of recombinant human tissue factor pathway inhibitor or adding granulocyte-colony-stimulating factor does not reduce mortality in patients with CAP.[82,83]

RECOMMENDED POLICY IN PATIENTS WITH PARAPNEUMONIC EFFUSION

Parapneumonic effusion (PPE) is defined as any pleural effusion associated with pneumonia. Parapneumonic effusion associated with loculations with or without pus and thickening of the pleura is called loculated parapneumonic effusion (complicated parapneumonic effusion). Empyema is defined as any pleural effusion with pus or micro-organisms in Gram stain or culture. In about 50% of cases empyema is caused by bacterial pneumonia. About half of the strains cultured from empyema are streptococci of the *S. intermedius ('milleri')* group and *S. pneumonia,* 20% are anaerobic pathogens and in 8% *S. aureus* is cultured.[84] Mortality of CAP increases if pleural effusion is present.[85] In patients with PPE with a significant quantity of pleural fluid, thoracocentesis should be performed to determine the pH and to send a sample for Gram stain and culture. Drainage of the pleural space is indicated in the presence of pus or PPE with a pH 7.2.[86] For patients in whom a loculated PPE is suspected, ultrasonography or chest CT should be performed.[87,88] In general intravenously administered antibiotics penetrate well in the pleural cavity[89,90] and installation of antibiotics into the pleural cavity is not recommended. Fibrinolytic therapy can be beneficial in selected cases of patients with loculated PPE and empyema, especially if the pleural fluid is not viscous, and fibrinolytic therapy is administered within 24 hours after admission.[91-94] Intrapleural fibrinolytic therapy does not reduce mortality in PPE and empyema, and does not improve the long-term functional or radiographical outcome.[92,95-97] When given, intrapleural fibrinolytic therapy should preferably be administered within 24 hours of admission. The most frequently used dosage regimen for intrapleural fibrinolytic therapy is streptokinase 250,000 IU or urokinase 100,000 IU once daily for three days. The chest tube should be clamped for two to four hours after administering the fibrinolytic agent. Surgical intervention should be considered as soon as it is clear that conservative treatment has failed, preferably within three days.

QUALITY INDICATORS FOR ANTIBIOTIC THERAPY IN CAP

Quality indicators must comply with high quality standards. Optimally, they should measure the quality in a valid and reliable manner with little inter- and intra-observer variability so that they are suitable for comparison between professionals, practices, and institutions. However, it should be emphasised that many current quality indicators are constructed based on relatively weak evidence and rather represent present best practices for CAP.[98] Reasonable process quality indicators for empirical antibiotic therapy in patients with CAP include the following: 1) rapid initiation of antibiotic therapy, 2) choosing an empirical antibiotic regimen according to national guidelines, 3) adapting dose and dose interval of antibiotics to renal function, 4) switching from iv to oral therapy, according to existing criteria and when clinically stable, 5) changing broad spectrum empirical into pathogen-directed therapy (streamlining therapy), 6) taking two sets of blood samples for culture, 7) using a validated scoring system (e.g. PSI score or CURB-65 score) to assess severity of illness, 8) urine antigen testing against *Legionella* spp. upon clinical suspicion and/or in severely ill patients. It should be emphasised here that these process quality indicators can be used as internal indicators in local quality improvement projects. It is not recommended

What's new: Top 5 changes in recommendations since the 2005 guidelines were published

- Concerns regarding increased antimicrobial resistance have grown in recent years. Notably, the resistance of *S. pneumoniae* to macrolides (10%) and doxycycline (7 to 11.5%) has increased, which limits the use of these agents for empirical treatment of CAP
- A urinary antigen test for *S. pneumoniae* should be performed in all patients hospitalised with severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached. Because of its low sensitivity, a negative test result does not justify broadening of empirical antibiotic therapy when no other pathogen is detected and the patient is clinically stable
- If adult patients with mild to moderate-severe CAP are treated with a β-lactam antibiotic or fluoroquinolone, the length of antibiotic treatment can be shortened to five days in those patients who improve substantially after three days of treatment. Procalcitonin (PCT) measurements are useful for shortening the duration of antibiotic therapy in patients with CAP who are treated for ten days or more. It is not recommended to use the PCT test to tailor the duration of antibiotic therapy in patients with CAP when standard treatment duration is limited to five to seven days
- During annual epidemics of influenza, which usually occur from late fall to early spring in the Netherlands, infection with this virus should be considered in patients presenting with CAP. PCR results from nasopharyngeal swabs are considered the most reliable indicator for influenza virus replication in the human body. Antiviral treatment is recommended for patients with confirmed or suspected influenza who have complicated illness, for instance pneumonia. Oseltamivir is the recommended antiviral medication of choice as recent viral surveillance and resistance data indicate >99% susceptibility among currently circulating strains. If CAP occurs directly following an episode of influenza, the influenza should also be treated pending results from PCR testing. In cases of fulminant pneumonia after an episode of influenza, penicillin should be replaced by a beta-lactam antibiotic with activity against *S. aureus*
- Concerns have arisen about potential unintended consequences of implementation of the rule that in patients with suspected CAP antibiotics be started within four hours of admission. Although these guidelines emphasise the importance of rapid administration of the first dose of antibiotics, maximal effort should be made that this recommendation does not cause the inaccurate diagnosis of CAP and/or inappropriate utilisation of antibiotics

that these indicators be used as external (performance) indicators to compare hospitals, as long as they have not been validated for this purpose.

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